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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,146	09/16/2002	Wilhelm Amberg	51748	9829

38939 7590 10/31/2008

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
10/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,146	AMBERG ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/11/08 has been entered.

2. Claims 4 and 10-12 are pending are under consideration in the instant application as they read on an a pharmaceutical composition for the treatment or prevention of cardiovascular diseases comprising an ETA endothelin blocker and an αvβ3 integrin receptor antagonist and a trade package thereof.

3. Applicant's IDS, filed 9/11/08, is acknowledged.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 4 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* (all of record).

Kirchengast *et al* teach 8 endothelin blockers such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 that were tested in different models of restenosis (a cardiovascular disorder) in rats and pigs. Kirchengast *et al* also teach that both the selective ET_A receptor antagonist FR 139317 and the mixed $ET_{A/B}$ receptor antagonist TAK 044 were able to reduce neointima proliferation by 76% and 80%, respectively. Further, the balanced $ET_{A/B}$ receptor antagonist SB 209670 was shown to reduce the neointima/media ration by 52%. Furthermore, BMS 182874 and LU135252 were able to reduce neointima/media ration by 35% and 25%, respectively (see page 552 under Endothelin antagonism in experimental restenosis and table 1 in particular).

The claimed invention differs from the reference teachings only by the recitation of a pharmaceutical composition, comprising an endothelin blocker and an αvβ3 integrin receptor antagonist in claim 4.

However, Srivatsa *et al* teach that selective αvβ3 integrin blockade potently limits neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury (a cardiovascular disorder). Srivatsa *et al* also tested the effect of the XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic αvβ3 antagonist on neointimal hyperplasia and lumen stenosis in a porcine coronary injury model (see age 424, 2nd col., at the end of the 2nd paragraph in particular). Srivatsa *et al* concluded that in large animal coronary stent restenosis model, use of a selective high affinity αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia and lumen stenosis (see page 426, last paragraph in particular).

Claim 11 is included because claim 11 recites the same products and the intended uses do not carry patentable weight per se and the claims read on the active or essential ingredients of the ET_A endothelin blockes and αvβ3 integrin receptor antagonists.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the endothelin blockers taught by Kirchegast *et al*, with the selective αvβ3 integrin antagonist XJ 735 taught by Srivatsa *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the endothelin blockers are able to reduce neointima proliferation (i.e., restenosis) as taught by Kirchengast *et al* and because the αvβ3 antagonist resulted in a marked reduction in neointimal hyperplasia the leading cause of restenosis. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 9/11/08, have been fully considered, but have not been found convincing.

Applicant submits that neither Kirchengast nor Srivatsa, alone or in combination teach, "A pharmaceutical composition for the prevention of restenosis comprising an ET_A endothelin blocker and an αvβ3 integrin receptor antagonist." Rather, Kirchengast teaches the use of endothelin receptor antagonists alone for the reduction of restenosis, and does not teach or suggest combining an ET_A endothelin blocker and an αvβ3 integrin receptor

antagonist for the prevention of restenosis. Kirchengast teaches, by way of summary of previously published data, that several different endothelin antagonists have been tested in different models of existing restenosis in live animals. These results are summarized in Table 1 (page 553), where Kirchengast discloses that the endothelin receptor antagonist FR 139317 reduced neointima proliferation by 76% and that the endothelin receptor antagonist TAK 044 reduced neointima proliferation by 80%. It is taught on page 553 (right bottom paragraph) that a blockade of the endothelin receptor is responsible for the reduction of restenosis. Given the high degrees of reduction in neointimal proliferation exhibited by certain of the endothelin receptor antagonists described, one skilled in the art extracts the clear teaching that administration of an endothelin receptor antagonist itself, in the absence of any other compound, is alone sufficient to reduce restenosis. However, there is no indication in Kirchengast to use αvβ3 integrin receptor antagonists for the prevention of restenosis.

Applicant submits that Srivatsa teaches αvβ3 integrin blockade limiting neointimal hyperplasia and lumen stenosis following deep coronary arterial stent injury and does not teach or suggest combining an ET_A endothelin blocker and an αvβ3 integrin receptor antagonist for the prevention of restenosis. Srivatsa teaches that a blockade of αvβ3 integrin limits stenosis. It is stressed in multiple passages that this blockade is selective (see abstract, page 424 left middle, 426 left middle). Therefore, the αvβ3 blocking compound, XJ 735, inhibits only αvβ3 and nothing else. Srivatsa further teaches that selective αvβ3 antagonism is sufficient to inhibit neointimal growth and lumen stenosis. Accordingly, if αvβ3 antagonism is alone sufficient to inhibit neointimal growth and lumen stenosis, and the compound XJ 735 used in the study is selective for only αvβ3 this mean that use of an αvβ3 integrin receptor antagonist alone already solves the posed problem of reducing restenosis. Faced with this teaching, one skilled in the art learns that inclusion of any other compound is unnecessary to solve the posed problem. Thus, Srivatsa teaches away from combining another substance with an αvβ3 integrin receptor antagonist in reducing restenosis, since this problem is already solved by an αvβ3 integrin receptor antagonist alone. Srivatsa does not mention endothelin blockers and there is no suggestion or motivation in Srivatsa to combine its αvβ3 integrin receptor antagonist with an endothelin blocker as Applicants have done in order to prevent restenosis.

Applicant concludes that Kirchengast and Srivatsa teach that administration of either an endothelin receptor antagonist or an αvβ3 integrin receptor antagonist alone already sufficiently solves the problem of reducing restenosis. This being the case, one skilled in the art would not contemplate adding another compound. If one compound is already sufficient to treat a given disease, it is illogical, and indeed impractical from a regulatory standpoint, to introduce another compound into the mix. Even if one skilled in the art could theoretically have combined the teachings of Kirchengast and Srivatsa, one skilled in the art would not have, and would have instead relied on the justifiable assurance that either the endothelin receptor antagonist of Kirchengast or the αvβ3 integrin receptor antagonist of Srivatsa would adequately solve the posed problem alone. Applicants submit that the reconstruction of the prior art to obtain Applicants' claimed invention requires impermissible hindsight.

The essence of Applicants' invention lies in the nonobvious combination of an endothelin receptor antagonist and an αvβ3 integrin receptor antagonist to achieve a sysnergistic effect in preventing restenosis. Applicants' invention permits the use of each component at a dose less than the dose useful alone, with a reduction in side effects (see specification, page 4, lines 23-27 and page 20, lines 24-30). Applicants' Example 5 (page 17, line 46 to page 18, line 6) shows that "the combination of ET receptor antagonists and αvβ3 integrin receptor antagonist represent a more effective means of preventing restenosis than treatment with either drug alone. In fact, given the higher predictive value of the pig restenosis model, the in vitro results suggest effective prevention of human restenosis with combinations of ET receptor antagonists and αvβ3 integrin receptor antagonist only, rather than monotherapy." This example clearly demonstrates that a combination of an endothelin blocker and an αvβ3 integrin receptor antagonist reduces coronaria restenosis in a pig model and therefore such combination is a factual basis for the prediction made in the claims and such combination has a clear synergistic effect. The present example provides factual support for the synergistic combination of an endothelin blocker and an αvβ3 integrin receptor antagonist for the prevention of restenosis.

Regarding Applicant's argument with respect to prevention, the examiner notices that obviousness can be established for achieving the claimed product for different reasons and the prior art/examiner does not need to know all of the properties of the claimed invention In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990); however there must be some suggestion or motivation. Therefore, the reason or motivation to combine may often suggest doing what the inventor has done, but for a different purpose or to solve a different problem than that asserted by the inventor. See MPEP 2144.

With respect to the desirable level improvement (reduction of neointima proliferation), the examiner point out that the desirable level improvement for the skilled in the art would be 100% not 76% or 80% as applicant argues. Further, the Examiner notes that the TAK 044 is $ET_{A/B}$ antagonist not ET_A endothelin blocker as claimed. Accordingly, one skilled in the art would be motivated to combine the ET_A blocker and the $\alpha v\beta 3$ integrin receptor antagonist to achieve a higher level of reduction of neointima proliferation to target the 24%/20% of reduction that was not achieved by the single administration of the ET_A endothelin blocker.

With respect to the "selective" blockage and "sufficient" to inhibit neointimal growth and lumen sternosis. The Examiner notes that the selective blockage refers to lack of crossreaction with other adhesion molecules (see page 425, right col., 2nd ¶). Further, the term sufficient is defined to be 43% reduction in the neointimal area (see page 421, Fig. 7 and section 3.3). Given that only 43% reduction is achieved by the $\alpha v\beta 3$ selective antagonist, the skilled in the art would be motivated to combine the $\alpha v\beta 3$ integrin receptor antagonist with the ET_A endothelin blocker antagonist to achieve higher neointimal hyperplasia and lumen sternosis reduction. The resultant combination would clearly be expected to be more efficient that the use of each compound individually. Given that both ET_A endothelin blocker and $\alpha v\beta 3$ integrin receptor antagonist inhibit neointimal growth and lumen sternosis but through different mechanism of action, synergistic therapeutic effects may occur.

It is the Examiner's position that in the absence of actual data and specific ET_A endothelin blocker and $\alpha v\beta 3$ integrin receptor antagonist, example 5 is a prophetical example. Applicant's reliance on a "synergistic effects" to distinguish its invention from prior art, using language suggesting the existence of actual clinical results even though such results had never been achieved. Speaking in the past tense, the example 5 states that "The findings show that the combination of ET receptor antagonists and $\alpha v\beta 3$ integrin receptor antagonists represent a more effective means of preventing restenosis than treatment with either drug alone. In fact, given the higher predictive value of the pig restenosis model, the in vitro results suggest effective prevention of human restenosis with combinations of ET receptor antagonists and $\alpha v\beta 3$ integrin receptor antagonists only, rather than monotherapy." that "[t]he study was performed in land race pigs applying PTCA.." and that "antagonist or a combination thereof was administered intravenously…" that "At the end of the experiments the LAD was excised" and that "[a]ll animals will receive an i.v. bolus injection of a tenth of the oral dose just before the angioplasty". See *Novo Nordisk Pharmaceuticals, Inc., et al. v. Bio-Technology General Corp., et al.* (Fed. Cir. October 5, 2005).

This is a simulated or predicted test results "clear synergistic effect" and prophetical examples (paper examples). No working examples correspond to work actually performed and describe tests which have actually been conducted and results that were achieved. Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted. Paper examples should not be represented as work actually done. No results should be represented as actual results unless they have actually been achieved. Paper examples should not be described using the past tense. Again, mere conclusions in the specification that the claimed combination had an unexpectedly a more effective means of preventing restenosis than treatment with either drug alone are not entitled to the weight of conclusions accompanying the statistical data or evidence in a declaration. See MPEP 716.02(a)-(c). Further, Example 5 is generic to all blockers and antagonists, however, the prior art is specific for both the blockers and antagonists. Dosages of receptor antagonists can vary depend on the half life of the antagonist and type of antagonist such as peptide, antibody, small organic molecule, nucleic acid or carbohydrate. Evidence has to be in the same scope as the prior art. The evidence has to show as much as the prior art.

6. Claims 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirchengast *et al* in view of Srivatsa *et al* as applied to claims 4 and 11 above, and further in view of US Pat. No. 4,761,406 of record.

The teachings of Kirchengast *et al* and Srivatsa *et al* have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a trade package (kit) comprising as pharmaceutical agent, an endothelin blocker and an αvβ3 integrin receptor antagonist together with an instruction for use of the pharmaceutical agents in claim 10.

The `406 patent teaches kits which facilitate the necessary strict compliance with methods of treatments (e.g., see col., 1, lines 9-12; col., 2, lines 24-26, and columns 13-15 in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the endothelin blocker such as BQ 123, SB209670, BMS 182874, TAK 044, FR 139317, LU 135252, Bosentan, A 1277225 and LU135252 taught by Kirchengast *et al* and αvβ3 integrin receptor antagonist such as XJ 735, a cyclic Arg-Gly-Asp (RGD) peptidomimetic taught by Srivatsa *et al* in a kit to facilitate the necessary strict compliance with methods of treatments

One would have been motivated to assemble the endothelin blocker and the αvβ3 integrin receptor antagonist in a kit format for conveniently and effectively implementing the method of treatment as taught by the `406 patent.

It is noted the only active ingredient in the claimed trade package (kit) is the endothelin blocker and the αvβ3 integrin receptor antagonist. Although the kits comprise instructions, there is no patentable weight given to the instructions themselves. It would have been prima facie obvious

to the ordinary artisan to include a piece of paper in the kit identifying the components therein at the time the invention was made.

It is noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a). Also, see In re Haller 73 USPQ 403 (CCPA 1947), where application of printed matter to old article cannot render article patentable and In re Venezia 189 USPQ 49 (CCPA 1976), where kits are drawn to the structural attributes of interrelated component parts and not to activities that may or may not occur. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. In re Casey , 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 9/11/08, have been fully considered, but have not been found convincing.

Applicant submits that neither Kirchengast, Srivatsa, nor Flora, either alone or in combination teach the claimed package. Rather, as discussed above, Kirchengast teaches only the use of endothelin receptor antagonists, and Srivatsa teaches only the use of $\alpha v\beta 3$ integrin receptor antagonists. Flora teaches a method and kit for treating or preventing osteoporosis. There is no teaching or suggestion in Kirchengast or Srivatsa to combine their respective endothelin receptor antagonists or $\alpha v\beta 3$ integrin receptor antagonists with the kit of Flora to obtain Applicants' claimed invention. Thus, it would not be obvious to combine Kirchengast, Srivatsa and Flora to arrive at Applicants' claimed invention.

It remains the Examiner's position that the combined reference teachings arrived to the claimed invention as delineated above.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 22, 2008

/Maher M. Haddad/
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